ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

1949

243 CHARLES STREET

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REPORTING the Laboratory's activities of the year is always accompanied by a measure of pride and humility. Again I have to report that no world-shaking discovery has been made and no cure-all for blindness has been found, but I do have the considerable satisfaction to report that what has been done has been done well and has advanced the humane cause in which the Laboratory is engaged to the full capacity of its present facilities.

For the purposes of simplification, the research activities are considered under the headings of Laboratory Sciences and Clinical Sciences, as has been our custom, but in point of fact there is no such clear-cut distinction. On the contrary, it is the prime policy of the Howe Laboratory to fuse the two, and any such division must necessarily be arbitrary and incomplete.

Laboratory Sciences

Glaucoma, the most frequent cause of permanent blindness, is an ever present challenge to ophthalmic investigators. Despite abundant descriptions of its pathology, the cause of glaucoma is still largely obscure. In recent years studies with the newer physiologic techniques have advanced our knowledge considerably of the basic factors involved in aqueous humor dynamics, and investigations in the Howe Laboratory have played a conspicuous role. Especially noteworthy during the past year have been Dr. Kinsey's studies on the mode of entrance and exit of various constituents of the aqueous humor and the osmotic relationships between the fluids in the posterior chamber, anterior chamber, and the blood plasma.

Experiments were performed to determine the mode of entrance of ascorbic acid, a substance which exists in the aqueous humor in relatively high concentration compared with that in the blood. Evidence was obtained which indicated that this substance is secreted as such into the posterior chamber and not as dehydroascorbic acid, its first oxidation product, as has been previously postulated in the literature. By means of a special technique for sampling aqueous humor in the posterior chamber, developed in conjunction with Dr. Cogan, it was shown that the concentration of ascorbic acid in the posterior chamber is about one and one-half times that in the anterior chamber. This suggests that the lens utilizes ascorbic acid in

its metabolism rather than preserving it in the anterior chamber, as was previously thought.

A study of the relative osmotic pressures in the aqueous humor taken from the anterior chamber, the posterior chamber, and the blood of rabbits showed that the osmotic pressure of the aqueous humor from the anterior and posterior chambers was the same but, as in man, is approximately 4 millimols of sodium chloride equivalent higher than in the blood. These results support the idea that the intra-ocular pressure is, in part at least, determined by the difference in tonicity between the aqueous humor and plasma.

A study was made of the chemical composition of the aqueous humor in comparison with that of the plasma withdrawn at the same time. This kind of information might be expected to clarify which constituents are responsible for the excess osmotic pressure in the aqueous humor, which enter the posterior chamber from the blood as a result of a secretory mechanism, and which simply diffuse between the blood and the aqueous humor in the posterior chamber. The total molar concentration due to all of the constituents present in the aqueous humor and blood was determined by measuring the osmotic pressure of these fluids. Chemical analyses were performed on a sufficient number of the constituents to account for approximately ninety-nine per cent of the total molarity. The results suggest that bicarbonate, because of its relatively high concentration in the aqueous humor compared with that in the plasma, is probably secreted, and because of its absolute concentration may play a dominant role in the entrance of the positively charged ion, sodium. Sodium, too, appeared to be in excess in the aqueous humor, provided the effects of the Donnan equilibrium were taken into account in making the calculations. The significance of these observations in formulating a general theory as to the formation of aqueous humor awaits further work.

Other information on the nature of the fluids in the posterior chamber has shown that the chloride concentration in the posterior and anterior chambers is essentially the same.

A by-product of these studies has been the development of a method for using the Beckman spectrophotometer for microanalytical purposes including the measurement of osmotic pressure in biological fluids.

It is of interest in connection with the work on aqueous humor that two groups of Swiss workers reported recently that the rate of turnover of water and the rate of flow of aqueous humor in man are essentially identical with those found some years ago in rabbits by the Howe Laboratory group.

Along an entirely different approach but directed toward the same end is a study by Dr. Grant on what he terms "tonography" in which the rate of change of intra-ocular pressure and volume is determined in response to certain extra-ocular pressures. This study utilizing electrical recording over a period of several minutes gives promise of providing valuable data on the aqueous outflow and inflow in human eyes and will be especially valuable in elucidating the hydrostatic functions in glaucoma and the influence on them of drugs and surgery. While still in the laboratory stage of development, it should ultimately contribute greatly to the understanding of glaucoma and its therapy.

Adding to the contributions which he has already made to the pharmacologic treatment of glaucoma, Dr. Grant in conjunction with Dr. Robert Trotter has further investigated the ophthalmic pharmacology and toxicology of compounds related to choline. The actions on the pupil, accommodation, cornea and conjunctival blood vessels of animal and human eyes were investigated in twenty-two compounds of the Reid Hunt Collection which were made available by Professor Krayer of the Department of Pharmacology. The ocular effects of most of these compounds had not previously been studied. Several instances of moderate miotic and cyclotonic activity were found, as well as instances of inversion of this effect with production of some mydriasis and cycloplegia. However, the compounds investigated appeared to have insufficient activity to be of therapeutic promise.

A new compound with exceptionally high and pure muscarinic activity, which had previously been studied in the Laboratory, was put to clinical trial in the treatment of glaucoma. This substance was a cyclic acetal quarternary ammonium compound which had been previously prepared and studied pharmacologically in France. When employed topically on glaucomatous eyes it was found highly effective in lowering the intraocular pressure in several instances, but the presence

of unpleasant systemic effects appears to limit its usefulness. Samples of the material synthesized in the Howe Laboratory have been furnished to Dr. Carr of the Department of Pharmacology for further investigation relative to its systemic pharmacology.

A compendium has been prepared by Dr. Grant in conjunction with Dr. Trotter of all that has been published on the effect of short-chain aliphatic quarternary ammonium compounds on the mammalian eye, assembling information previously available only from scattered sources. This group of compounds is characterized primarily by miotic activity, and several of the antiglaucoma drugs in current use have come from this group.

The experimental technique for the objective optical measurement of fluorescent substances in the eye has been further refined by Dr. Ludvigh. This refinement has resulted in an increase of sensitivity by a factor of twenty and should enable the rate of flow of aqueous humor to be determined with an observation period as short as two minutes. It will, of course, be necessary to have the human eye either remain fixed for two minutes or be repositioned with sufficient accuracy after a previous measurement.

Dr. Ludvigh has revised and issued in mimeographed form two more sections to his *Introduction to Ophthalmic Optics*. One section is a detailed discussion of visual acuity; the other is a section on color vision.

For cultivating the ocular lens *in vitro*, Drs. Merriam and Kinsey have developed a technique which is suitable for making quantitative investigations of the chemistry of normal and cataractous lenses. Lenses cultured by this technique show few gross evidences of abnormality after a period of several weeks and maintain a relatively normal carbohydrate metabolism during this period. By introducing the amino acid, glycine, labeled with radioactive carbon, it was shown that the lens synthesizes glutathione, a substance which is apparently necessary for normal transparency of the lens, since its concentration is known to be greatly diminished in all forms of cataract. The results indicated that half of all the glutathione in the lens is renewed in the normal rabbit lens in about thirty-five hours.

Similar studies made on cataractous lenses produced by feeding rabbits naphthalene showed that the decreased con-

centration of glutathione was due to an interference with the synthesizing mechanism. In these lenses over seventy hours are required to synthesize half of the glutathione present, even though the total amount of glutathione present in these lenses may be only about one-tenth that found in normal lenses. Preliminary experiments suggest that there is a relatively rapid "turnover" of the protein and lipids in the normal lens. These studies are being pursued at the present time under contract with a program sponsored by the Atomic Energy Commission.

As part of his overall study of toxicology of the eye, Dr. Grant tested the effect of repeated paracentesis on the course of ammonia burns in the rabbit eye, since the impression had been gained by some that this was effective in human beings. The eyes of a series of rabbits were exposed to ammonium hydroxide at dosage levels such as to produce both mild and severe burns, and some of the eyes were treated by paracentesis within a few minutes and daily thereafter, but no significant beneficial effect was found in comparison with the untreated eyes. It thus is apparent that the practice of paracentesis in human beings has little experimental justification in the treatment of ammonia burns of the eye.

Also as part of his toxicological studies, specifically in regard to the investigation of methyl alcohol poisoning, Dr. Grant found that the substance tetraethylthiuram disulfide did not appreciably increase the toxicity of either methyl alcohol or of ethyl alcohol in the rabbit. This compound, known as "Antabus" when it is used in the treatment of alcohol addiction, is known to increase the toxicity of ethyl alcohol in human beings through hindering oxidation beyond the acetaldehyde stage.

Clinical Sciences

The use of radioactive substances as a tool and as an end in itself has become in recent years common practice in various laboratories throughout the world. Since the pre-war studies on formation of aqueous humor by Kinsey, Grant and Cogan, which were the first use of tracer elements in ophthalmic research, the Howe Laboratory has become increasingly involved in problems of radiation. Recently the Atomic Energy Commission has made two grants to the Howe Laboratory for the

study of radiation cataracts. One of these grants will be used to support an investigation by Drs. Kinsey and Merriam of various biochemical alterations in the lens following exposure to radiation, and the other grant will be utilized by Drs. Cogan and Donaldson to study the cataractogenic dose and morphogenesis of radiation cataracts in animals.

The present accentuation of interest in radiation cataracts is prompted in considerable measure by the discovery during the past two years of cataracts in young physicists who had been exposed to radiations in what had been thought to be "safe dosages" from the cyclotron. Since the types of ionizing radiation from the cyclotron, neutrons and gamma rays, are similar to those which were emitted by the atomic bombs, it seemed of considerable interest and some importance to determine whether radiation cataracts had occurred in the survivors of the atomic bombing. Accordingly, the National Research Council sent Dr. Cogan with Dr. S. Forrest Martin of Boston and Dr. Samuel J. Kimura of San Francisco to Japan for the purpose of setting up an Eye Clinic in conjunction with the Atomic Bomb Casualty Commission to make a survey of the surviving population. Approximately 2,000 persons were examined. Ten patients were found with radiation cataracts, showing an incidence of about two per cent of the sample of survivors who had been within 1 kilometer of the hypocenter at the time of the explosion. All had been severely epilated within a few weeks after the bombing, but radiation sickness was not constantly present. Persons who had been farther from the hypocenter than 1 kilometer had varying degrees of epilation and thermal burns and gave histories compatible with having had keratitis from ultraviolet radiation, but none were found who had radiation cataracts.

A review of radiation effects on the eye was prepared by Dr. Cogan and presented at a Symposium conducted by the Section on Ophthalmology at the annual meeting of the American Medical Association, and a treatise on the ocular effects of radiation sickness has been prepared for a forthcoming book in England entitled *Systematic Opthalmology*.

Parallel with the foregoing, Dr. Grant presented at the Symposium of the Section on Ophthalmology of the American Medical Association a synopsis of the chemical, physical and

physiological aspects of chemical burns of the eye and prepared a section on ophthalmic toxicology for the projected book *Systemic Ophthalmology*, considering the subject from the symptomatic standpoint.

During the past year the results of treatment of sixty glaucomatous patients with tetraethyl pyrophosphate were analyzed by Dr. Grant. This drug appears to be equal in effectiveness to the di-isopropylfluorophosphate which is frequently used but resulted in a number of cases of local hypersensitivity.

For a Symposium on Primary Chorioretinal Aberrations with Night Blindness held during the past year by the American Academy of Ophthalmology and Otolaryngology, Dr. Cogan prepared the portion dealing with patho-histology of the condition. This report centered about specimens from five cases of retinitis pigmentosa which were obtained for study from the Army Institute of Pathology, the Wilmer Ophthalmological Institute and the Massachusetts Eye and Ear Infirmary, two cases of choroideremia obtained from Dr. McCulloch of Toronto and Dr. Reese of New York, and a variety of allied conditions, many of which were grouped under the heading of pseudoretinitis pigmentosa and obtained largely from the Massachusetts Eye and Ear Infirmary. The differential criteria were outlined, and as much information on the pathogenesis as could be obtained from histologic evidence was presented. As a conclusion of the study it was suggested that further investigation should be made of the utilization of vitamin A by the retina in patients with retinitis pigmentosa. In anticipation of such a study, Dr. Donaldson has built a dark adaptation apparatus for the clinical testing of patients with retinitis pigmentosa. Whether or not any profitable leads will be turned up remains to be seen, but at the outset it is worth noting that even the remotest possibility is worth while pursuing, for this is one of the most tragic diseases, almost inevitably leading to blindness in its cruelly relentless manner.

An exhibit accompanying the foregoing symposium and containing among other items some of the pathologic material that had been collected was awarded first prize at the Academy's convention.

The activities of the Retina Service have been considerably expanded under the direction of Dr. Charles Schepens, who holds a joint appointment in the Howe Laboratory and Massachusetts Eye and Ear Infirmary. A detailed fundoscopic study was made of 345 patients with detachment of the retina, and operations were done on 167 patients. Among the many observations and tentative conclusions, the following appear especially noteworthy. Massive vitreous retraction was found in about five per cent of the patients, a condition that was often precipitated by diathermy; detachments of the choroid following operations for retinal detachment are not infrequent and do not require further surgery; detachments of the retina of the ora type may be caused by inflammatory lesions near the ora serrata and are frequently accompanied by mild anterior uveitis, lenticular opacities in the posterior cortex, and deep chamber glaucoma.

An interesting, though unsuccessful, experiment on the removal of non-magnetic intra-ocular foreign bodies was undertaken during the past year by Drs. Cogan and Grant in conjunction with the Navy. The patient in question had received in both eyes multiple intra-ocular foreign bodies of a non-magnetic material from the explosion of a detonating cap. It was decided that surgery was out of the question, and the only hope appeared to be a new high frequency technique that had been developed by the Metamagnet Company. An experimental model of the apparatus was obtained, and the appropriate power was provided by the Submarine Signal Division of the Raytheon Manufacturing Company. Failing to get satisfactory results, the inventors, Drs. William V. Lovell and Winifred Lovell, were flown to Boston from Florida and spent several days in a futile effort to obtain sufficient pull ("g" force) on the particles of the size and composition of those that were within the eyes. Although not promising, the method was believed to be sound, and further attempts are being made to develop an apparatus having the requisite output, and correlative measurements have been made by Drs. Rich and Roth of the Raytheon Manufacturing Company on the mechanical inertia of the vitreous and by Dr. Grant on the power of the ordinary giant magnet. If successful, the method would be a great boon, for most eyeswith non-magnetic intra-ocular foreign bodies are currently lost.

A simple procedure for temporarily closing the eyelids was described by Dr. Cogan during the past year. This consists of using some viscous adhesive (e.g. Du pont "Duco cement") which forms a cast over the closed lids. The closure lasts several weeks and is less disfiguring and more easily applied than the lid sutures which have been customarily employed. The method is especially useful for exposure keratitis accompanying transient facial palsy or that occurring in comatose patients who have insufficient closure of the lids.

Finished during the past year were pathologic studies by Dr. Cogan of a case of endogenous intra-ocular fungus infection. The organism was thought to be aspergillus and is the sixth case of such an infection to be recorded in the literature. As in the five other similar cases, no systemic source of the fungus was found.

A technique has been developed by Drs. Cogan and Donaldson for measurement of the anteroposterior dimensions of structures in the anterior segment of the living eye with an accuracy of a few hundredths of a millimeter. This is currently being employed to study the variation in corneal thickness in normal and diseased eyes. It is hoped to define more accurately some of the variations that occur in this structure with local and systemic disease. One of the practical difficulties in making these measurements is to maintain the eye sufficiently immobilized during the test. For this purpose an aid has been devised using a mirror before the eye which is not being examined and permitting either steady fixation or controlled movement of the eye under ready manipulation.

Collaboration of the Howe Laboratory with other hospital and university departments has often proved profitable. One of these collaborative studies during the past year has been the study of unilateral internuclear ophthalmoplegia through the conjoint interests of the Departments of Neurology, Ophthalmology, and the Howe Laboratory. A series of patients have been obtained showing this rare condition, and for the first time one case was studied pathologically. Serial sections of the brain stem in this latter case showed the causative lesion to be a necrotic area involving the medial longitudinal fasciculus on one side. This case and presumably the others were due to

vascular lesions; this is of especial interest, since the more common entity of bilateral internuclear ophthalmoplegia is rarely of vascular origin. A report is in preparation by Drs. Cogan, Charles Kubik and William Smith.

Dr. Kinsey has continued to direct the study on retrolental fibroplasia conducted by the Massachusetts Eye and Ear Infirmary. From a clinical point of view these studies have been concerned chiefly with determining the effect on the incidence of retrolental fibroplasia of omitting from the feeding of premature infants certain vitamins which had previously been administered, and with the therapeutic use of vitamin E in those infants who appear to be developing this disease. It is too early to draw definite conclusions from these studies. Experimental studies have been continued on the influence of various dietary supplements on the plasma level of alpha tocopherol and the symptoms of vitamin E deficiency in experimental animals.

Photography of the eye has been a profitable side issue of the Howe Laboratory and a worth-while investment from a teaching and research point of view. The Laboratory has accumulated and filed an impressive series of pictures, both still and moving pictures, that with few restrictions are loaned out to the staff of the Infirmary and others for instructional purposes. Beginning with black-and-white microphotography which Dr. Verhoeff did largely himself, then experimentation in the early days of color photography by the late Dr. Berger, and more recently the use by Drs. Trotter and Grant of the electronic flash for illumination, the technique has been further improved in the past year by the color stereophotography of Dr. Donaldson. Using two cameras and separate lens systems which he has devised and constructed, the results are the best that have ever been attained in eye photography and vie with biomicroscopy for visualization of the anterior segment of the eye. An exhibit of some of Dr. Donaldson's pictures was held at the Howe Library in conjunction with one of the New England Ophthalmological Society meetings.

Teaching

The teaching of the Basic Science Course in Ophthalmology for postgraduates at the Harvard Medical School was again largely done by the staff of the Howe Laboratory without major change from previous years except as follows. The teaching of neuro-ophthalmology was greatly enhanced by brain dissections which Dr. Donaldson had prepared in the Laboratory and photographed utilizing his new stereoscopic technique. Dr. Grant extended considerably the course on Pharmacology and Toxicology and withdrew from some of the teaching of Introduction to Clinical Procedures.

Lectures were also given by Dr. Grant to the undergraduate class in Pharmacology of the Harvard Medical School and to the Simmons College Orthoptic class.

The policy of incorporating basic scientists in the Howe Laboratory was developed during the past year along a new channel. For the first time a candidate for the Ph.D. degree did his thesis work in the Howe Laboratory. This was a joint venture with the Chemistry Department of Boston University and was supervised locally by Dr. Kinsey. The candidate was Frederick C. Merriam, and the subject of his thesis was Synthesis of Glutathione in the Ocular Lens. Dr. Merriam has since been appointed to the staff and will continue his studies at the Laboratory under the auspices of the Atomic Energy Commission. It would appear that this type of training serves well the dual function of indoctrinating basic scientists in eye research and giving them an awareness of the opportunities in a quasi-clinical field. It is hoped to continue the system as space facilities and promising candidates are available and to offer similar opportunities for selected individuals who have had a primarily clinical training.

Under the guidance of Miss Jeanette Loessl, the Lucien Howe Library has maintained a high standard of service to the ophthalmic and medical community. A departure from previous custom is now under contemplation whereby the Library will also serve the Ear, Nose and Throat Department.

Past and Future

During the past year Dr. Burwell resigned as Dean of the Harvard Medical School and was succeeded by Dr. George Berry. To orient himself, the new Dean requested a description of the various departments outlining the accomplishments of the past and plans for the future. The letter is reprinted here in the hope and belief that it may be of general interest.

December 20, 1949

Dr. George Berry
Harvard University Medical School
25 Shattuck Street
Boston, Massachusetts

Dear Dr. Berry:

Your letter of November 15th requesting a description of the organization and aims of the Howe Laboratory gives me a welcome opportunity to acquaint you with us and our endeavors.

The Howe Laboratory has been in existence approximately twenty years. It was established by moneys given by Dr. Lucien Howe, the General Education Board and Harvard University. The endowment approximates $700,000 with a current income of about $30,000. The founding of the Laboratory and its history through the first ten years of its existence is presented in an article by Harry K. Messenger which appeared in the Harvard Medical Alumni Bulletin of January, 1937. The more recent history of the Laboratory is obtainable from our Annual Reports. A list of the publications of the Howe Laboratory and the available reprints through 1940 is available in bound form in the Harvard Medical School Library and in the Howe Library. Those which have appeared since 1940 are available at the Howe Laboratory and are listed in the accompanying enclosure.

The present Laboratory occupies approximately 2,000 square feet at the Massachusetts Eye and Ear Infirmary and is currently divided into five rooms. Heat and light are provided by the Infirmary, but all other expenses are paid by the Laboratory. The present staff consists of seven investigators, one on an appointment without limit of time, three on three-year term appointments, and three on one-year term appointments. The major subjects represented by these investigators are ocular physiology, biochemistry, physiologic optics, pharmacology, toxicology, clinical ophthalmology and neuro-ophthalmology. The specific accomplishments that have come from the Laboratory are too numerous to cite in detail, but I believe it is fair to say they are considered to be top quality, and some of them represent major advances. The Howe Laboratory is currently cited as one of the few pioneer organizations of its kind in the world. Some of the fields of its original research have been the clinical physiology

of the cornea, aqueous humor, and lens; binocular perception; the pharmacologic control of abnormal intra-ocular pressure; the pathologic response to certain industrial chemicals and to the harmful effects of radiant energy; and a study of ocular manifestations of neurologic disease. During the war, special contributions were made in the fields of dynamic stereopsis and of the effects of war gases on the eye and tissue in general. Moreover, a system of postgraduate education in the basic sciences in ophthalmology was begun by the Howe Laboratory and has become a model for many such courses now being given.

The opportunity afforded to the Howe Laboratory is that of bridging the basic and clinical sciences in problems related to the eye. Having necessarily different criteria, and even a different vernacular, these two sciences are often worlds apart when faced with a specific problem. Only by bringing the two together at a close operational level can there be an effective interchange of ideas and methods. What the basic scientist has to offer the clinician is not so much the single answer to a specific problem as the opening up of new vistas that may not have occurred to the clinician, and what the clinician has to offer the basic scientist is not merely the practical application on human beings of theoretical and experimental observations on animals but also the stimulus for new down-to-the-earth problems and an awareness of the limitations, as well as the possibilities, of research on human beings. To these ends the Howe Laboratory is well adapted, since it is a division of the Harvard Medical School which has plentiful academic resources and is situated in the Massachusetts Eye and Ear Infirmary with a wealth of clinical material and contacts at its disposal. In keeping with this policy, two of the four continuing staff members have been trained primarily in the basic sciences and carry the degree of Ph.D., whereas two have been trained primarily in the clinical sciences and carry the degree of M.D.* This has enabled considerable collaboration between the Laboratory and various university departments and hospitals.

The problems of the Howe Laboratory in its struggle for existence are money, space and certain administrative restrictions. These will be briefly discussed seriatim.

The income of $30,000 falls far short of maintaining the present financial commitments of the Laboratory involving seven full-time staff members, four full-time technicians, one secretary, one porter, as well as the cost of supplies and equipment. In addition the Howe Laboratory has paid the salary of one full-time librarian and half the cost of books and journals for the Howe Library. The income would have scarcely been able to support such an organization before the war and is patently unable to do so with the currently reduced purchasing power of the dollar in the postwar inflation. Accordingly, informal appeals have been made for donations, and to date it has

* The present organization of the Howe Laboratory has been well described by V. Everett Kinsey, Ph.D. in an article entitled Fundamental Research in the Clinical Specialties which appeared in *Science* 105; 373 (1947).

been possible to maintain the Laboratory's precarious existence on a pre-war standard by the beneficence of certain organizations (Massachusetts Eye and Ear Infirmary, American Optical Company), foundations (John and Mary Markle Foundation, Snyder Foundation, the Eye Bank for Sight Restoration, Inc.), government agencies (Office of Naval Research, Office of Scientific Research and Development, Atomic Energy Commission) and personal grants (ophthalmologists and patients). With grants from these sources the income of the Laboratory has been almost doubled but, as you know, much of this is "project money" which must be used for purposes other than the maintenance of the Laboratory. Valuable as support of this kind is, it should not be confused with the long-term support of fundamental research which is our prime function. What the Howe Laboratory needs more than anything else is additional endowment. It is submitted that a laboratory of the size and importance of the Howe Laboratory should have an income of $60,000–$100,000 annually. For this an endowment of $2,000,000 is needed, and that is our financial goal.

Space is currently our second problem. At the inception of the Howe Laboratory 2,100 square feet was offered to it by the Infirmary, but it was the expressed intention of both parties that a separate building would ultimately be obtained. In recent years the present quarters which are approximately equivalent to those originally offered to it have become wholly inadequate. The present cramped conditions result not only in considerable inefficiency in operation but greatly restrict the number of opportunities for following up new leads or providing services which would otherwise be possible. The responsibility of providing space for an expanded laboratory was never clearly defined in the original agreements, and it would now appear that anything over and above the 2,100 square feet must be provided for by a special gift. A laboratory double the present size is our space goal.

Certain administrative restrictions comprise our third problem. As a department, the Howe Laboratory is unusual, if not unique, in the Harvard curriculum. It is a research department, allied to clinical medicine, without definite teaching responsibilities, aimed at pioneering in the ophthalmic sciences. To accomplish this most effectively it has had to develop a species of career investigator who necessarily becomes a specialist within a specialty. Whether the recent policies of the Harvard Medical School regarding tenure and postgraduate teaching will act to the advantage or disadvantage of the Howe Laboratory remains to be seen. In any case they do force us to reconsider the desirability of continuing "career" investigators and have removed much of the flexibility for development of postgraduate teaching in ophthalmology. It is suggested that the recent regulations which are undoubtedly suitable for the usual teaching departments that have considerable turnover of personnel and necessarily operate on a pyramidal system are less adaptable for the peculiarities of a research unit such as the Howe Laboratory.

I cannot begin to cite the tremendous possibilities of an expanded laboratory devoted to research on the eye. Few disasters can compare with the tragedy of blindness, and yet so little money has been available for its study in a research laboratory; so little fundamental information has been discovered even for the normal eye; and such limited facilities have been available where investigators can and will devote their full attention to research on the eye. To maintain and expand these possibilities seems to me clearly one of the greatest investments in medical research at the present time and comprises an altogether logical request. Compare, for instance, the $2,000,000 which is requested for a permanent endowment with the $40,000,000 spent *annually* in the United States for the care and rehabilitation of the blind, or compare the 4,000 square feet of floor space requested as research quarters with that used for the clinical care of the ophthalmic patient. Moreover, I know of no place where the history of its past or promise for its future would serve the purpose of expansion more effectively than in the case of the Howe Laboratory of Ophthalmology.

Sincerely yours,

David G. Cogan, M.D.

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Acknowledgement

Again it is a pleasant task to thank the many who, in one way or another, have furthered the functions of the Howe Laboratory during the past year, and an especial expression of gratitude is in order to the following organizations and individuals who by their generosity have made possible the balancing of the budget.

The Massachusetts Eye and Ear Infirmary, for general expenses.

American Optical Company, for the support of research in physiologic optics.

The Eye-Bank for Sight Restoration, Inc., New York City, for studies on lens metabolism.

The Snyder Foundation, for studies on aqueous humor.

Atomic Energy Commission, for studies on radiation cataracts.

Paul A. Chandler, M.D., for general expenses.

Edwin B. Dunphy, M.D., for general expenses.

Mrs. Alfred Meyer, for general expenses.

Henry A. Mosher, M.D., for general expenses.

Mr. and Mrs. David B. Turner, for general expenses.

Dr. F. A. Donaldson, M.D., for general expenses.

Board of Surgeons in Ophthalmology, for operating expenses of the Library.

David G. Cogan, M.D.
Director

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